LEADING ARTICLE

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Female Sexual Dysfunction

Potential for Pharmacotherapy

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Abstract

The act of sex includes a woman's sexual self and self-image, intimate relationships, family, society and culture. The complexities of her environment, sexual and partner history, past relationships, mental health status, current medical problems and hormonal status all play a role. An interdisciplinary consensus conference panel expanded the former Diagnostic and Statistical Manual of Mental Disorders-IV classifications of female sexual dysfunction to include psychogenic and organic causes of desire, arousal, orgasm and sexual pain disorders that cause personal distress.

The US FDA Guidance paper details the recommendations for the clinical development of drugs for the treatment of female sexual dysfunction. In this document, great emphasis is placed on orgasm as a clinical trial endpoint and it would appear that satisfactory sexual intercourse is of secondary importance to the Agency. However, there is no evidence to suggest that the majority of women correlate their sexual enjoyment and satisfaction with numbers of orgasms or even the likelihood of orgasm during a given sexual interaction. Nonetheless, any drug coming through the regulatory agency in the US will need to follow these recommendations.

Currently, there are six major pharmaceutical therapeutic paths being pursued for treatment of female sexual disorders and/or postmenopausal symptoms. These include dopaminergic agonists and related substances, melanocortin-stimulating hormones, adrenoceptor antagonists, nitric oxide delivery systems, prostaglandins, and androgens. A number of compounds that target these pathways are undergoing development for female sexual dysfunction. The array of pharmacological agents that are being developed for female sexual dysfunction must prove to be efficacious and have a good safety profile at a time when there are increasing worries that hormonal replacement with estrogen and progestogens are not safe. It is unclear if any of these pharmaceutical pathways will prove to be both safe and effective for the treatment of female sexual disorders; however, studies investigating this area will provide important scientific data for the future.

Experts in the field of female sexual dysfunction often start a lecture with a comical picture demonstrating the difference between sexual responses of males and females. Figure 1, an example of this picture, shows two gadgets with switches. Gadget one is a simple on-off switch representing the male sexual response. Gadget two is a complicated device with switches of various colours and sizes. It is of no surprise that this represents the female sexual response. This picture demonstrates the complexity of female sexual function and the problems identifying appropriate therapy.

The act of sex includes a woman's sexual self and self-image, intimate relationships, family, society and culture. The complexities of environment, sexual and partner history, past relationships, mental health status, current medical problems and hormonal status all play a role.[1] It has yet to be clearly determined what critical neuroendocrine mechanisms or hormonal metabolic pathways play a role in female sexual response. Emotional intimacy, as described by Basson,[2] may be an important underpinning. A healthy relationship with a partner, good general health of both partners, freedom from severe life stresses, and absence of financial worries are all important factors.

1. Definition

An interdisciplinary consensus conference panel,[3] consisting of 19 experts in female sexual dysfunction, developed consensus definitions and classifications for female sexual dysfunction, building on the existing framework of the WHO International Classification of Disease-10 (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) of the American Psychiatric Association. The former DSM-IV classifications were expanded to include psychogenic and organic causes of desire, arousal, orgasm and sexual pain disorders. An essential element of this new diagnostic system is the personal distress criterion, meaning that a condition is considered a disorder only if it creates distress for the woman experiencing the condition.[3] A woman's personal perspective alone should govern the diagnosis and the provider must not impose his/her interpretation on a woman's experience. The outcomes of the consensus method have been called into question,[4] but this method continues to be important in raising issues of definitions and future research. Currently, there is an ongoing re-evaluation of the current definitions of the female sexual response cycle in conjunction with the 2nd International Consultation on Erectile and Sexual Dysfunctions.[5]

Fig. 1. A comical depiction of the difference in sexual responses between men (top) and women (bottom).

1.1 Sexual Desire Disorders

Hypoactive sexual desire disorder is the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for, or receptivity to, sexual activity, which causes personal distress.[3,6] Under the new classification system, a patient's perception of personal distress or deficiency is crucial to the diagnosis of sexual desire disorders, as well as other sexual disorders.[3] Synonyms for sexual desire are sexual appetite, libido, sexual drive, sexual impulse and sexual interest. These all refer to the main sexual appetitive feeling that motivates a woman to obtain sex and focus her attention on that goal. An absence or deficiency of libido is another way of characterising lack of sexual desire.

1.2 Sexual Arousal Disorders

Female sexual arousal disorders (FSAD) include the persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress.[2,6] It may be expressed as a lack of subjective excitement or a lack of genital lubrication/swelling or other somatic responses. However, it would appear that the vast majority of women diagnosed with FSAD, delineated no further, may show a healthy normal increase in pelvic vasocongestion in response to an erotic stimulus when measured in the laboratory using a vaginal photoplethysmography.[2] However, vaginal vasocongestion during erotic stimulus with the use of sildenafil may not be associated with the personal perception of arousal improvement.[2]

Arousal disorders can include a wide range of disorders. No sub-groups of FSAD are formally recognised, for example, those lacking subjective arousal despite normal genital vasocongestive response and those with lack of physiological engorgement. Empirically, the administration of estrogen is an important treatment for post-menopausal women with associated vaginal atrophy.[7]

1.3 Orgasmic Disorders

An orgasmic disorder is 'the persistent or recurrent difficulty, delay in or absence of attaining orgasm following sufficient sexual stimulation and arousal, causing personal distress'.[3] Implicit in this definition is an acceptance that if a woman does not have a release during her experience of arousal and this lack of release is not distressing to her, then it is not dysfunctional.

1.4 Sexual Pain Disorders

Sexual pain disorders include dsypareunia, vaginismus and non-coital sexual pain disorders.[3] These important disorders interfere with satisfactory sexual intercourse and orgasm. Currently, there is no drug therapy for these disorders and the presence of these disorders have been exclusion criteria in all current clinical trials evaluating outcomes of desire, arousal and/or orgasm.

1.5 Alternative Cycles

More recently, Dr Rosemary Basson[2] has offered an alternative cycle of female sexual response, which emphasises the emotional component in female sexual desire. Basson[2] suggests that it is often a desire for increased emotional intimacy with her partner, rather than the 'sexual hunger' posited in traditional models of sexual response, that predisposes a woman to engage in sexual activity, especially in longer term relationships. Sexual stimuli and their context are fundamental ingredients of a woman's sexual response. Once stimulated, a woman can move from what was a state of sexual neutrality to one of sexual arousal. Stimuli from the external environment and the emotional experience of arousal feeds into the central nervous system (CNS), that is, the paralimbic areas of the CNS, and then to the appropriate spinal cord receptors. The somatic or bodily response of genital congestion or arousal feeds back into the paralimbic areas. The

importance of this feedback appears to be highly variable. It may also be negatively evaluated.[8] Basson[2] also points out that an additional cycle of emotional response acts on sexual centres, such as the medal pre-optic area of the hypothalamus and other limbic and paralimbic structures.

2. Prevalence

Most studies suggest that sexual dysfunction is more prevalent in women than in men regardless of the countries included or assessment tools used. It is important to remember that prevalence data is dependent on the assessment techniques and these have been highly variable. A comprehensive literature review by Simons and Carey[9] notes an overall prevalence of the following disorders: desire disorders 5–46%; arousal disorders 7–10%; and orgasmic disorders 7–10%. The most often quoted study notes a sexual dysfunction prevalence of 43% in women versus 31% in men.[10,11] This same study noted that, of this 43%, an estimated 22% were thought to have low sexual desire defined as lack of interest in sex. In 1978, Frank et al.[12] noted sexual dysfunction in 35% of women versus 16% of men. In this same study, 63% of affected women reported arousal or orgasmic dysfunction, and 77% reported difficulty that they defined as not dysfunctional in nature (e.g. lack of interest or inability as inferred by self-reported frequency of sexual thoughts, fantasies, dreams, wishes and interests in initiating and/or engaging in sexual experiences).

Cross-sectional results from the Massachusetts Women's Health Study II indicated a decreased sexual desire among married women, those with psychological symptoms, current cigarette smokers and perimenopausal status.[13,14] The National Council on Aging survey notes that sexual activity plays an important role in relationships for older women.[15] In healthy women it would appear that the prevalence of sexual dysfunction declines with age.[14] The frequency of sexual intercourse has been shown to be inversely related to depression, physical limitations of a partner and smoking, but not related to menopausal status.[16] Depression and associated drug therapy are the most common biological factors that inhibit sexual arousal.[17,18]

Taken together, all the data are suggestive of a high prevalence of sexual dysfunction in women.

3. Outcome Measurements

3.1 Pathophysiology

What is a deficiency disease and how should it be defined? A deficiency disease should be based on two major premises: (i) that the deficiency can be defined; and (ii) that the disease or syndrome responds to appropriate analyte replacement or therapeutic intervention which can be measured.[19] Endocrine deficiency diseases such as diabetes mellitus and hypothyroidism have been well characterised because of glucose changes and thyroid deficiency, respectively. Defining sexual dysfunction based on deficiency of an analyte, e.g. androgens, has not been as easy.

3.2 Physiological Measurements

The design and inclusion of valid, reliable, non-invasive and acceptable endpoints to measure outcomes of clinical trials assessing female sexual dysfunction is complicated. Many of the objective measurements of sexual response are not patient-friendly. Two examples include magnetic resonance imaging (MRI) technology and photoplethysmograph devices. Vaginal photoplethysmograph devices are the size of a tampon measuring blood flow or vaginal engorgement following response to visual sexual stimulation. Although vaginal photoplethysmography and pelvic MRI have provided important scientific data it is not clear whether this data is well correlated with self-reports of genital lubrication.[20-22] The use of these devices is also expensive.

Despite the drawbacks associated with pelvic MRI and vaginal photoplethysmography, the data extrapolated from clinical trials using such devices have provided important clinical information for future trials.

3.3 Quality-of-Life Questionnaires

Disease-specific quality-of-life instruments must be stringently developed and validated prior to use in clinical trials in accordance with US FDA guidelines.[23] Several measurements have recently been published and include the Female Sexual Function Index (FSFI),[24] the Female Sexual Distress Scale (FSDS),[25] and the Sexual Function Questionnaire (SFQ).[26] The FSFI was supported by Zonagen, Inc. and Bayer AG. It is a 19-item questionnaire assessing six domains including desire, subjective arousal, lubrication, orgasm, satisfaction and pain. The SFQ, developed by Pfizer for clinical trials, is a 31-item survey that measures seven domains of female sexual function (desire, enjoyment, orgasm, arousal/sensation, arousal lubrication, and pain and partner satisfaction). An important addition that is currently in development is the FSDS; distress is characterised as an essential component of female sexual dysfunction. See also the recent review of validated methods by Rosen.[27]

3.4 The US FDA Guidance Paper

The FDA guidance paper[23] for the clinical development of drugs for the treatment of female sexual dysfunction will be an important regulatory requirement for conducting clinical trials in this area. In this document, the FDA recognises four components of sexual response, treating each as individual components without understanding the complexity and current thinking of female sexual function. This guidance paper places great emphasis on orgasm as a clinical trial endpoint and it would appear that satisfactory sexual intercourse, as a clinical endpoint, is of secondary importance to the Agency. However, there is no evidence to suggest that the majority of women correlate their sexual enjoyment and satisfaction with numbers of orgasms or even the likelihood of orgasm during a given sexual interaction. In addition, it assumes valid and reliable diagnostic measurements distinguishing women with and without the disorder, and places little emphasis on the importance of coexisting elements associated with female sexual dysfunction, for example, depression and drug therapy.[28,29] Individuals may, in fact, vary in their propensity for both sexual excitation and inhibition.[30] Any emphasis on coexisting and contextual problems must be identified as inclusion or exclusion criteria. No emphasis appears to be placed on the role of drug therapy as either initiators or conditioners of sexual response.[31]

4. Pharmacological Treatment Options

What is in the pharmaceutical pipeline for the potential treatment of female sexual dysfunction? There are no currently approved drugs for the treatment of female sexual dysfunction, and any new drug coming through the regulatory agency and the Division of Reproductive and Urologic Drug Products will need to follow recommendations of the FDA.[23] There are six major pharmacological paths of interest related to female sexual dysfunction. These include dopaminergic agonists and related substances, melanocortin-stimulating hormones, adrenoceptor antagonists, nitric oxide delivery systems, prostaglandins (smooth muscle relaxants) and androgens. Table I summarises the classes of drugs and expected intended uses within female sexual dysfunction for each class.

4.1 Dopaminergic Agonists

The use of dopaminergic drugs, when given to patients with Parkinson's disease, was thought to have a stimulatory effect on sexual behaviour in some recipients.[28,29] Moreover, patients who re-

Table I. Potential treatments being developed for female sexual dysfunction

Drug mechanism of action	Probable indication	Product	Developing company (phase of development)
Dopamine receptor agonist	Desire	Intranasal apomorphine	Nastech/Pharmacia (phase II)
Nonselective α_1- and α_2-adrenoceptor antagonist	Arousal	Oral phentolamine	Zonagen (phase I)
Nitric oxide system			
Phosphodiesterase IV inhibitor	Arousal	Sildenafil	Pfizer (phase II)
	Arousal	Tadalafil	Lilly/ICOS (phase II)
Other nitric oxide donors	Arousal	Arginine + yohimbine	NitroMed
α-Melanocyte stimulating hormone analogue	Desire and arousal	PT-141	Palatin (phase I)
Prostaglandins (smooth	Arousal	Alprostadil topical gel	Vivus (phase II)
muscle relaxant)	Arousal	Alprostadil topical	Nexmed
Androgens			
Testosterone	Desire	Transdermal testosterone	Watson/Proctor & Gamble (phase III)
		Testosterone gel	Cellegy
Estrogen/androgen combination	Desire	Esterified estrogen/methyltestosterone[a]	Solvay
Androgenic dietary supplements	No claims for an indication (NRR)	Multiple androgen substances	Multiple sources
Natural products	No claims for an indication (NRR)	Zestra™[b] for women[c]	Qualilife

a Indicated for the management of moderate to severe vasomotor symptoms associated with menopause in patients who do not respond to estrogens alone.

b Use of tradenames is for product identification only and does not imply endorsement.

c This product has been deemed as 'generally recognised as safe' and is available via the internet.

NRR = no regulatory review.

ceived bupropion for the treatment of selective serotonin reuptake inhibitor (SSRI)-induced sexual adverse events reported experiencing an increase in libido.[32] Selective activation of dopamine D_2 receptors in the medial preoptic area by the systemic administration of dopamine agonists, e.g. apomorphine, increased the sexual behaviour of rats and rhesus monkeys at doses which did not elicit other responses.[33-36] Dopamine appears to be an activating neurotransmitter while serotonin is an inhibitor.[37]

Quinelorane (Eli Lilly and Company) was one of the early drugs in the dopaminergic class that was being developed for inhibited sexual desire and arousal.[28] However, the development of this compound has been abandoned.

A sublingual formulation of a nonselective D_1 and D_2 dopamine receptor agonist, apomorphine (TAP Pharmaceuticals), has been approved in Europe and is awaiting registration in the US for the treatment of erectile dysfunction. Unconfirmed rumours suggest the development of an apomorphine product for female sexual dysfunction.

Nastech is developing an intranasal formulation of apomorphine for the treatment of both male and female sexual dysfunction. Although the use of dopamine agonists in sexual dysfunction is a promising research area, no other dopaminergic agents appear to be in development for female sexual dysfunction.

4.2 α-Melanocyte-Stimulating Hormone

Recent findings indicate that effects on sexual dysfunction may be stimulated through melanocortin receptors in the brain.[38-40] A nasally administered analogue of α-melanocyte-stimulating hormone, namely PT-141, is undergoing phase I trials with Palatin Technologies for the treatment of fe-

male sexual dysfunction.[41] Research suggests that it works through a mechanism involving the CNS.[39]

4.3 α-Adrenoceptor Antagonists

Phentolamine is a combined α_1- and α_2-adrenoceptor antagonist that was originally approved for the treatment of pheochromocytoma-induced hypertension and norepinephrine-related dermal necrosis. Phentolamine has been used off-label as an injectable intracavernosal injection therapy for erectile dysfunction. Zonagen, Inc. has developed a new rapid-release oral formulation of phentolamine for the treatment of female sexual dysfunction. The effects of oral phentolamine 40mg were assessed in a placebo-controlled, pilot study of six postmenopausal women with lack of lubrication or subjective arousal during sexual stimulation.[40] Only mild improvements in subjective (self-reported arousal) and objective (changes in vaginal blood flow assessed using vaginal photoplethsysmography) measures of sexual arousal were observed in response to visual sexual stimulation (two 20 minute erotic videotapes). Similar findings have been reported by other studies assessing the use of oral phentolamine in the treatment of female sexual dysfunction.[42,43] Currently, no further studies are planned.

Combinations of pharmaceutical agents, similar to those in development for male sexual dysfunction, have been suggested for use in female sexual dysfunction. One such combination was the simultaneous use of phentolamine and alprostadil (prostaglandin E_1) cream. However, these studies appear to have been abandoned. To date, there are no scientific studies evaluating this combination in female sexual dysfunction. At the October 2001 Female Sexual Function Forum in Boston, Massachussetts, USA, a preliminary small study using phentolamine and apomorphine was reported.[42] There was inadequate data on either compound singularly or in combination to comment on either safety or efficacy.

4.4 Prostaglandins

There is a long history of using prostaglandins for male sexual dysfunction and, specifically, erectile dysfunction.[44] This class of drug is perceived to have an effect for some women with genital sexual arousal disorder by presumably relaxing the vaginal arterial smooth muscle and increasing vaginal secretions. It has been assumed that an important reason for genital arousal difficulties in women, especially postmenopausal women, is decreased blood flow and associated decreased vaginal lubrication with arousal. However, the phenomenon of reduced lubrication in estrogen-deficient women is far from straight forward and warrants further studies in order to clarify the problem.

At the 2002 American Urological Association meeting in Orlando, Florida, USA, researchers from Vivus presented the in-clinic evaluation of a topical formulation of alprostadil for the treatment of female sexual dysfunction.[45,46] The placebo-controlled study included 79 postmenopausal women with sexual arousal disorder. The history of these women was not clear (e.g. the number of vaginal deliveries each women had undergone). A local application of alprostadil 100 or 400μg resulted in a significant improvement over placebo in both somatic sensations associated with sexual arousal, and in subjective reports of sexual arousal and satisfaction with arousal in the 120 minute period following visual sexual stimulation. The women who received alprostadil 400μg reported significantly greater changes from baseline for endpoints of genital warmth, tingling, level of sexual arousal, satisfaction with sexual arousal and sexual satisfaction.

NexMed is developing an alprostadil-based formulation using a permeation enhancer to deliver the drug vulvally.[47] The indication for this product will be women with sexual arousal disorder. Three phase I clinical trials have been completed, which have tested the safety of this product at different dosages in 70 premenopausal women. A phase II study has

been conducted in premenopausal women and another phase II study is expected to begin in 110 postmenopausal women with sexual arousal disorder. The efficacy of this alprostadil formulation will be assessed with diaries, patient questionnaires (i.e. FSFI and the FSDS) as well as a global assessment questionnaire.

4.5 Nitric Oxide Facilitators

While the role of nitric oxide[48] and nitric oxide facilitators (e.g. phosphodiesterase IV inhibitors such as sildenafil[49]) in facilitating penile erection is well understood, much less is known regarding the role of nitric oxide and phosphodiesterase inhibitors in female sexual arousal.

4.5.1 Phosphodiesterase Inhibitors

Several phase I and II studies have assessed the use of sildenafil in the treatment of female sexual dysfunction. Laan and colleagues[50] randomised 12 healthy premenopausal women without sexual dysfunction to receive a single oral 50mg dose of sildenafil or matching placebo in the first session and alternate medication in a second session. Although sildenafil was found to be effective in enhancing vaginal engorgement during erotic stimulus conditions, the changes were not associated with an effect on subjective sexual arousal.

In a randomised, placebo-controlled study, Basson et al.[51] were unable to demonstrate that sildenafil 10–100mg was efficacious in improving subjective arousal in either estrogen-replete or estrogen-deficient (pre- and postmenopausal women with sexual disorders that included, but were not limited to, arousal disorders). The genital physiological effect of sildenafil was not perceived as improving the sexual response in either group of women, as assessed using a 31-item sexual function survey, global efficacy questions, the life satisfaction checklist and an event log of sexual activity.

Several other small studies that have compared sildenafil with placebo have raised more questions. Kaplan et al.[52] studied 33 postmenopausal women with sexual dysfunction but did not demonstrate significant improvements in overall sexual function. Caruso et al.[53] found that there was an improvement with sildenafil in frequency of orgasm compared with placebo using a nonvalidated questionnaire. Sipski et al.[54] randomly assigned 19 spinal cord injured (SCI) premenopausal women to sildenafil 50mg or placebo in a crossover design. The effects of sildenafil on sexual arousal and desire were most evident under conditions of both visual and manual stimulation, consistent with previous findings in SCI men. It will remain to be seen whether there are special populations of women who respond to sildenafil.[52-54] Similar to the results obtained with sildenafil, exploratory trials with tadalafil in premenopausal women have failed to conclusively demonstrate sexual arousal.[55]

4.5.2 Other Nitric Oxide Donors

NitroMed's lead product is a patented combination of the nitric oxide donor arginine (L-arginine) and yohimbine, a competitive α_2-adrenoceptor receptor antagonist.[56] This product has successfully completed Phase I and IIa trials in the US and France, respectively, for female sexual dysfunction and has demonstrated no drug interactions with nitrates in a further series of pharmacological trials. There are no ongoing studies with this product in this indication at this time.

ArginMax™[1] is a proprietary nutritional supplement consisting of extracts of ginseng, ginkgo, damamiana, arginine, and vitamins and minerals. In a 4-week, placebo-controlled study, women receiving ArginMax™ reported an improvement in sexual desire, clitoral sensation and satisfaction with their overall sex life, a reduction of vaginal dryness and an increase in frequency of sexual intercourse and

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

orgasm without any significant adverse effects.[57] More stringent scientific studies will be needed for this interesting combination of supplements.

4.6 Androgens

For a long time, researchers of sexual dysfunction have claimed that it is an androgen deficiency disease[1,58] and suggestions for treatments have included a variety of androgens (e.g. testosterone, dihydrotestosterone, dehydroepiandrosterone [DHEA], androstenedione and androgenic dietary supplements) in a variety of formulations (e.g. pellets, injectables, formulated creams). Androgens are listed as teratogens resulting in masculinisation of the external genitalia of the female fetus during critical developmental periods.[59-61] No studies have determined effects in the human male fetus. Conventional wisdom is that aromatisable androgens do not pass from the maternal to the fetal circulation, although this has not been documented.

To date, there have been no population-based studies demonstrating a correlation between a deficiency in testosterone or DHEA and a sexual desire disorder in women. If there is a correlation, it must be based on a general deficiency in androgen levels associated with a sexual desire disorder and/or an improvement in sexual desire disorder associated with androgen replacement.[19] At the 2001 Princeton Meeting in Princeton, New Jersey, USA, a group of scientists evaluated the peer-review literature and they defined female androgen insufficiency as consisting of a pattern of clinical symptoms in the presence of decreased bioavailable testosterone and normal estrogen status.[62,63] The Princeton Report Summary[62] noted a lack of analytical sensitivity and reliability at androgen levels consistent with an androgen deficiency disease. Therefore, without a diagnostic test to assess androgen deficiency it is difficult for clinicians to treat the disease in women. Bancroft[64] has noted that the current 'understanding of the effects of androgens on human sexuality is far from complete, particularly in the female'.

Findings from the Women's Health Initiative Clinical Trial,[65] which found increased health risks with accepted hormone replacement therapies (e.g. estrogen and progestogen), might raise similar concerns regarding androgen replacement without definitive evidence.

4.6.1 Testosterone

Phase III studies have been initiated for the specially designed transdermal testosterone patch for female sexual dysfunction (developed by Watson Pharmaceuticals/Theratech and trialled by Proctor and Gamble). In a phase II study, 75 (65 completers) surgically-induced menopausal women with impaired sexual function who were receiving standard estrogen replacement therapy were randomised to the testosterone patch (150 or 300μg) or placebo.[66,67] The strong placebo response tended to mask further effects of testosterone. That is, scores for the frequency of sexual activity and pleasure-orgasm on the Brief Index of Sexual Functioning for Women were 72, 74 and 81 for placebo, testosterone 150μg and testosterone 300μg, respectively; only the 300μg testosterone patch was superior to placebo. The 300μg testosterone patch also increased feelings of positive well-being and improved mood. The benefit over placebo was primarily observed in older patients (≥48 years [n = 34]) receiving the 300μg dose. There was no change in self-perceived problems affecting a woman's sexual function.

Cellegy has completed several phase I/II studies evaluating a transdermal testosterone metered gel product for female sexual dysfunction.[55] Although the sponsor notes that testosterone levels are restored to 'normal', it is unclear how they measured and determined what were normal testosterone levels for menopausal women. To date, there have been no published studies regarding the use of this testosterone gel product in women with sexual dys-

function, although continued development is planned.[68]

BioSante and Antares are also developing a gel formulation of testosterone for use in female sexual dysfunction.[69]

4.6.2 Estrogen/Androgen Combinations

Solvay has an estrogen/androgen combination consisting of esterified estrogen 1.25mg and methyltestosterone 2.5mg. It has been marketed since 1964 for menopausal syndrome. Menopause is associated with hormonal changes. Although the age-related loss of estrogen and progesterone are clear, the relationship between declining androgens and sexual function have not been clarified. A relationship between androgen levels and sexual function has not been determined.[58] Solvay is now investigating its use in female sexual dysfunction. To date, there are no published well-designed, placebo-controlled studies demonstrating the efficacy of this particular combination of estrogen/methyltestosterone with long-term use in this indication.[1,70]

4.6.3 Other Androgen Products

Several other companies have been developing other formulations of androgens for the potential use in female sexual dysfunction. Columbia Laboratories is developing a progressive hydration testosterone vaginal tablet for women with menopausal syndrome. In this indication, the product is intended to create a no-bleed menopause and shrink fibroids, and it may also enhance libido. However, it is unclear whether the progressive hydration testosterone vaginal tablet will have an indication for female sexual dysfunction.[55]

Solvay has begun Phase I studies with a testosterone gel for the treatment of postmenopausal symptoms.[55] Novavax, Inc. is developing a testosterone product for post-menopausal women.[55] A methyltestosterone patch is undergoing phase II development with Noven, Inc.[71]

In summary, there appear to be no shortage of companies developing androgens with and without estrogens for symptoms of menopause. However, whether these products will show promise in female sexual dysfunction remains to be seen.

It should be noted that many investigators believe that there is an interesting subset of peri- and premenopausal women deficient in adrenal androgens.[72-74] It is not clear if this deficiency disease will exemplify the population as a whole.

4.6.4 Androgenic Dietary Supplements

The passage of the 1994 FDA Dietary Supplement Health and Education Act (DSHEA)[75] allowed for the expanded availability of androgenic substances. Androgenic dietary supplements do not require regulatory review and have thus not undergone formal trials of efficacy and safety. In addition, a lack of manufacturing inspection has allowed contamination with more potent androgenic compounds may lead, for example, to positive nandrolone testing. DHEA and androstenedione are the two major androgen supplements currently available, although there is a growing number of 'pro-androgen' supplements being introduced to the marketplace either through the internet or in stores without prescription. Examples include: 4-androstene-3, 17-dione; 5-androstene-3, 17-dione; 4-androstene-3, 17-diol; 5-androstene-3, 17-diol; 19-nor-4-androstene-3, 17-dione; 19-nor-4-androstene-3,17-diol; 19-nor-5-androstene-3, 17-diol; and 5-androsten-3.β-ol-17-one (dehydroepiandrosterone/DHEA).

5. Herbal Remedies

Compounds that are made up of 'generally recognised as safe' (GRAS) substances require no regulatory review. One such product, Zestra™ for women (Qualilife Pharmaceuticals) is an oil that contains natural botanical ingredients (borage seed oil, evening primrose oil, special extracts of angelica, coleus forskolin, antioxidants and vitamin E) with natural fragrances. It has entered the internet market and

featured at the October 2001 Female Sexual Function Forum of the International Society for the Study of Women's Sexual Health in Boston, Massachussetts, USA.[76] Before market entry of Zestra™ the sponsor conducted a small, randomised, double-blinded, crossover study in 20 women, of whom, 10 had female sexual arousal disorder. Diary questions regarding satisfaction with arousal were used as primary efficacy endpoints. Secondary endpoints included diary questions. The study reported improvements relative to placebo in levels of arousal, desire, satisfaction and sexual pleasure. Zestra™ is meant to be applied (0.5–1mL) with gentle massage to the external female genitalia, clitoris, labia and vaginal opening at least 3–5 minutes prior to vaginal intercourse for enhanced sexual experience. Other herbal remedies can be found at sex boutique stores.[77]

6. Conclusion

The development of a drug that can be safely used in the treatment of female sexual dysfunction continues to be complicated. The array of neurotransmitter agonists and antagonists (e.g. dopaminergic agonists, adrenoceptor antagonists), nitric oxide delivery systems, smooth muscle relaxants (e.g. prostaglandins), and new hormonal formulations (e.g. melanocortin-stimulating hormones, prostaglandins and androgens) that are being developed for female sexual dysfunction must prove to be effective and have a good safety profile at a time when there are increasing worries that hormonal replacement with estrogen and progestogens are not safe. The field is further complicated by the interaction between the categories of sexual response (e.g. desire, arousal and orgasm) adding variance to outcomes that may be additionally magnified by learned behaviour (or placebo response) in clinical trials. It is unclear whether any of the major pharmacological paths currently being investigated in the treatment of female sexual dysfunction will result in safe and effective treatments. If it is possible to identify subpopulations who respond to a therapeutic regimen, the question will remain whether such regimens may be applied to the entire population. While the mechanisms underlying female sexual dysfunction still remain unclear, additional research will further elucidate the complexity of the female sexual repertoire, which will hopefully lead to safe pharmacological therapy.

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References

1. Fourcroy J. Issues and priorities in the development of drug treatments for female sexual dysfunction. Int J Impot Res 1998; 10 Suppl. 2: S121-S3
2. Basson R. Expand the concepts of the human sex response cycle. J Sex Marital Ther 2001; 27 (1): 33-44
3. Basson R, Berman J, Burnett A, et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classification. J Urol 2000 Mar; 163: 888-93
4. Bancroft J, Graham CA, McCord C. Conceptualizing women's sexual problems. J Sex Marital Ther 2001; 27: 95-103
5. Organization of medical consultations. ICUD – NGO in official relationship with the World Health Organization, International Society of Urology, and International Society for Sexual and Impotence Research [online]. Available from URL: www.congress-urology.org [Accessed 2003 Apr 16]
6. American Psychiatric Association. DSM-IV: diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Press, 1994
7. Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 1996 Apr; 23 (3): 259-63
8. Heiman JR. Female sexual response patterns: interactions of physiological, affective, and contextual cues. Arch Gen Psychiatry 1980 Nov 11; 37: 1311-6
9. Simons J, Carey MP. Prevalence of sexual dysfunctions: results from a decade of research. Arch Sex Behav 2001; 30 (2): 177-219

10. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States; prevalence and predictors. JAMA 1999; 281 (6): 537-44
11. Laumann E, Michael R, Michaels S, et al. The social organization of sexuality. Chicago (IL): University of Chicago Press, 1994
12. Frank E, Anderson C, Rubenstein D. Frequency of sexual dysfunction in normal couples. N Engl J Med 1978; 299: 111-5
13. Avis N, Stellato R, Crawford S, et al. Is there an association between menopause status and sexual functioning? Menopause 2000; 7 (5): 297-309
14. Avis N. Sexual function and aging in men and women: community and population-based studies. J Gend Specif Med 2000; 3 (2): 37-41
15. The National Council on Aging [online]. Available from URL: http://www.ncoa.org/content.cfm?sectionID=105&detail=128 [Accessed 2003 Apr 16]
16. Kingsberg SA. The impact of aging on sexual function in women and their partners. Arch Sex Behav 2002; 31 (5): 431-7
17. Clayton AH. Female sexual dysfunction related to depression and antidepressant medications. Curr Womens Health Rep 2002 Jun; 2 (3): 182-7
18. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999; 19: 67-85
19. Fourcroy JL. Androgens and desire pharmacology in women: syllabus and presentation. First Annual Comprehensive Review of Sexual Medicine; 2002 Apr 18-21; Vancouver
20. Deliganis AV, Maravilla KR, Heiman JR, et al. Female genitalia: dynamic MR imaging with use of MS-325: initial experiences evaluating female sexual response. Radiology 2002; 225 (3): 791-9
21. Heiman H. Presentation: psychophysiological measurement perspective. First Annual Comprehensive Review of Sexual Medicine; 2002 Apr 18-21; Vancouver
22. Laan E, Everaerd W. Physiological measures of vaginal vasocongestion. Int J Impot Res 1998 May; 10 Suppl. 2: S107-10
23. US Food and Drug Administration. Guidance for Industry. Female sexual dysfunction: clinical development of drug products for treatment [online]. Available from URL: http://www.fda.gov/cder/guidance/3312dft.htm [Accessed Apr 16]
24. Rosen R, Brown C, Heiman J, et al. The female sexual function index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000; 26: 191-208
25. Derogatis L, Rosen R, Leiblum S, et al. The female sexual distress scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. J Sex Marital Ther 2002; 28 (4): 317-30
26. Quirk F, Heiman J, Rosen R, et al. Development of a sexual function questionnaire for clinical trials of female sexual dysfunction. J Womens Health Gend Based Med 2002 Apr; 11 (3): 277-89
27. Rosen RC. Assessment of female sexual dysfunction: review of validated methods. Fertil Steril 2002; 77 Suppl. 5: S89-93
28. Crenshaw TL, Goldberg JP. Dopaminergic drugs. In: Crenshaw TL, Goldberg JP, editors. Sexual pharmacology. New York: WW Norton & Company, 1996: 369-88
29. Jensvold MF, Plaut VC, Rojansky N, et al. Sexual side effects of psychotropic drugs in women and men. In: Jensvold MF, Halbreich U, Hamilton JA, editors. Psychopharmacology and women. Washington, DC: American Psychiatric Press Inc, 1996: 323-68
30. Bancroft J. State of the art lecture: inhibitory mechanisms in men and women. First Annual Comprehensive Review of Sexual Medicine; 2002 Apr 18-21; Vancouver
31. Heaton J. New classification system for erectile dysfunction therapies. J Androl 1998; 19 (4): 399-404
32. Gitlin MJ, Sun R, Altshuler L, et al. Bupropion-sustained release as a treatment for SSRI-induced sexual side effects. J Sex Marital Ther 2002 Mar-Apr; 28 (2): 131-8
33. O'Sullivan JD, Hughes AJ. Apomorphine-induced penile erections in Parkinson's disease. Mov Disord 1998; 13 (3): 536-9
34. Foreman MM. Disorders of sexual response: pioneering new pharmaceutical and therapeutic opportunities. Expert Opin Investig Drugs 1995; 4 (7): 621-36
35. Alcantarra AG. A possible dopaminergic mechanism in the serotonergic antidepressant-induced sexual dysfunctions. J Sex Marital Ther 1999; 25 (2): 125-9
36. Foreman MM, Hall JL. Effects of D2-dopaminergic receptor stimulation on male rat sexual behavior. J Neural Transm 1987; 68: 153-70
37. Everaerd W, Laan E. Drug treatments for women's sexual disorders. J Sex Res 2000; 37 (3): 195-204
38. Wessells H, Gralnek D, Dorr R, et al. Effect of an alpha-melanocyte stimulating hormone analog on penile erection and sexual desire in men with organic erectile dysfunction. Urology 2000; 56 (4): 641-6
39. Wessells H, Fuclarelli K, Hansen J, et al. Synthetic melanotropic peptide initiates erections in men with psychogenic erectile dysfunction: double-blind, placebo controlled crossover study. J Urol 1998; 160 (2): 389-93
40. Rosen RC, Phillips NA, Gendrano NC. Oral phentolamine and female sexual arousal disorder: a pilot study. J Sex Marital Ther 1999; 25: 137-44
41. Palatin Technologies [online]. Available from URL: www.palatin.com [Accessed 2003 April 16]
42. Rubio-Aurioles E, Rampazzo C, Hurley D, et al. Combination therapy for female arousal disorder: a clinical trial to evaluate the efficacy of a combination of phentolamine mesylate and apomorphine in the subjective response to video sexual stimulation [abstract]. Female Sexual Function Forum; 2001 Oct 25-28; Boston (MA), 84
43. Rubio-Aurioles E, Lopez M, Lipezker M, et al. Phentolamine mesylate in postmenopausal women with female sexual arousal disorder: a psychophysiological study. J Sex Marital Ther 2002; 28 Suppl. 1: 205-15
44. Physicians Desk Reference (PDR). 57th ed. Montvale (NJ): Thomson PDR, 2003
45. Gittelman M, Costabile RA, Peterson C, et al. In clinic evaluation of the safety and efficacy of topical alprostadil (PGE1) for the treatment of female sexual dysfunction [abstract 603]. J Urol 2002; 167 (4): 151

46. Islam A, Mitchel JT, Rosen R, et al. Topical alprostadil in the treatment of female sexual arousal disorder: a pilot study. J Sex Marital Ther 2001; 27: 541-9
47. NexMed (USA), Inc. [online]. Available from URL: http://www.nexmed.com/press/news118.htm [Accessed 2003 May 29]
48. Krane R, Brock G, Eardley I, et al. Committee 8 oral non-endocrine treatment. In: Jardin A, Wagner G, Khoury S, et al., editors. Erectile dysfunction. Plymouth: Plymbridge Distributors Ltd, 2000: 730
49. Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction: Sildenatfil Study Group. N Engl J Med 1998; 338 (20): 1397-404
50. Laan E, van Lunsen RHW, Everaerd W, et al. The enhancement of vaginal vasocongestion by sildenafil in healthy premenopausal women. J Womens Health Gend Based Med 2002; 11 (4): 357-66
51. Basson R, McInnes R, Smoith M, et al. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. J Womens Health Gend Based Med 2002; 11 (4): 367-77
52. Kaplan SA, Reis RB, Kohn IJ, et al. Safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction. Urology 1999; 53: 481-6
53. Caruso S, Intelisano G, Lupo L, et al. Premenopausal women affected by sexual arousal disorder treated with sildenafil: a double-blind, crossover, placebo-controlled study. Br J Obstet Gynaecol 2001; 108: 623-8
54. Sipski ML, Rosen RC, Alexander CJ, et al. Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injuries. Urology 2000; 55: 812-5
55. Novavax, Inc. [online]. Available from URL: http://www.novavax.com/womens.html [Accessed 2003 May 29]
56. Meston CM, Worcel M. The effects of yohimbine plus L-arginine glutamate on sexual arousal in postmenopausal women with sexual arousal disorder. Arch Sex Behav 2002; 31 (4): 323-32
57. Ito T, Trant AS, Polan ML. A double-blind placebo-controlled study of ArginMax, a nutritional supplement for enhancement of female sexual function. J Sex Marital Ther 2001; 27 (5): 541-9
58. Basson R, Bourgeois-Law G, Fourcroy J, et al. Androgen 'deficiency' in women is problematic. Med Aspects Hum Sex 2001 Sep; 1 (6): 41-3
59. Grumbach MM, Ducharme JR, Moloshok RE. On the fetal masculination action of certain oral progestins. J Clin Endocrinol Metab 1959; 19: 1369-80
60. Kirk JM, Perry LA, Shand WS, et al. Female pseudohermaphroditism due to a maternal adrenocortical tumor. J Clin Encrocrinol Metab 1990; 70: 1280-4
61. Moore KL, Persaud T. The developing human. 6th ed. Philadelphia (PA): WB Saunders, 1998: 563
62. Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril 2002; 77 (4): 660-5
63. Bachmann G, Bancroft J, Braunstein G, et al. Androgen deficiency in women: definition, diagnosis and classification. Princeton Meeting; 2001 Jun 29; Princeton (NJ)
64. Bancroft J. Sexual effects of androgens in women: some theoretical considerations. Fertil Steril 2002 Apr; 77 Suppl. 4: 55-9
65. Women's Health Initiative Clinical Trial Writing Group. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002; 288 (3): 321-33
66. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 2000; 343 (10): 682-8
67. Mazer NA. Testosterone deficiency in women: etiologies, diagnosis, and emerging treatments. Int J Fertil 2002; 47 (2): 77-86
68. Cellegy Pharmaceuticals Inc [online]. Available from URL: http://www.cellegy.com/home.html [Accessed 2003 Apr 16]
69. Antares Pharma [online]. Available from URL: http://www.antarespharma.com/content/news/news_06062001.html [Accessed 2003 Apr 16]
70. Phillips E, Bauman C. Safety surveillance of esterified estrogens-methyltestosterone (estratest and estratest HS) replacement therapy in the United States. Clin Ther 1997; 19 (5): 1070-84
71. Noven Pharmaceuticals, Inc. [online]. Available from URL: http://www.noven.com/research.htm [Accessed 2003 May 29]
72. Arlt W, Callies F, Vlumen JCV, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999; 341 (14): 1013-20
73. Barnhart KT, Freeman E, Grisso JA, et al. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. J Clin Endocrinol Metab 1999; 84: 3896-902
74. Miller KK. Androgen deficiency in women. J Clin Endocrinol Metab 2001; 86: 2395-401
75. US Food and Drug Administration. Dietary Supplement Health and Education Act Public Law 103-417 1994 [online]. Available from URL: http://www.fda.gov/opacom/laws/dshea.html [Accessed 2003 Apr 16]
76. Ferguson D. Randomized, placebo-controlled, double blind, crossover design trial of the efficacy and safety of Zestra for women in women with, and without, female sexual arousal disorder. J Sex Marital Ther 2003; 29 (1): 33-44
77. Grand Opening [online]. Available from URL: http://www.grandopening.com/ [Accessed 2003 Apr 4]

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